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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,563	03/08/2001	Stuart B. Levy	PKZ-043	5356

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,563	LEVY ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-18, 20-24, and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,25,26 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11-3-200* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 1-18, 20-24, and 27-32 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the paper filed on November 3, 2003.

2. Currently, claims 19, 25, 26, and 33-38 are pending and under consideration to the extent that they read on the elected invention.

3. It is noted that Applicant appears to have interpreted the restriction among the subinventions of Group III as a species election. This is incorrect. The restriction in this case is a restriction among distinct inventions. However, it is also noted that the inventions all fall under the scope of claims 19, and 25. Thus, claims 19 and 25 are linking claims to the subinventions identified in claim 26. Therefore, as per USPTO linking claim practice (see, MPEP 809.03), the linking claims will be considered with the elected invention.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on November 3, 2003, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Specification

5. The disclosure is objected to because of the following informalities: the specification appears to refer to both NIMR polypeptides and genes by the gene identifiers. For example, nfnB, although known as the identifier of an E. coli gene, is used in the present application to represent the polypeptide. This is contrary to the customary use of the gene identifiers, and provides no means to distinguish between the genes and encoded polypeptides.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim reads on a method of using a NIMR polypeptide modulator to decrease the virulence of a microbe, and indicates that the NIMR polypeptide is to be selected from a provided list. However, the list provided appears to describe a number a genes rather than a number of polypeptides. See e.g., App., pages 7-8 (indicating that the terms listed in claim 26, including nfnB, represent genes from E. coli K-12, and not the polypeptides encoded therein. It is suggested that the claim be amended to read on methods wherein the NIMR polypeptide is encoded by a gene selected from the identified group.

8. Claims 19, 20, 25, 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on methods of reducing microbial virulence, or otherwise treating microbial infection through administration of a NIMR (newly identified MarA responsive gene) modulating agent. However, the specification defines NIMR genes (hence polypeptides) as excluding genes identified as part of the prior art regulon. Page 7. The specification further indicates that the prior art regulon "includes: acrAB, fumC, inaA, marA, marB, marR, ompF, ompX, soda, tolC, and zwf." Id. However, the specification does not indicate that this list identifies all of the prior art mar regulon genes. Nor does the application provide a complete list of, or a common structural characteristic of, molecules that are NIMR molecules. It is therefore unclear what genes do and do not fall within the Applicants definition of an NIMR gene or polypeptide as it is not clear what genes are included in the prior art.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 19, 25, 26, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As indicated above, the identified claims relate to the modulation of NIMR

polypeptides. The Applicant's definition of NIMR polypeptides is also described, in part, above. In addition to the definition provided above, the specification also indicates that NIMR genes and polynucleotides comprise molecules that are "structurally related" to one or more of the genes identified in Table 1 of the application, and that encode polypeptides "having an NIMR polypeptide activity." See, page 9, and page 22, respectively. Thus, the Applicant has attempted to identify a genus of inventions comprising the methods using modulators of NIMR molecules. The Applicant has not provided an adequate written description for the claimed invention because the application does not provide sufficient descriptive support for either a genus of the NIMR molecules themselves, or for the genus comprising modulators thereof.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed. It is noted that, in the instant case, the Applicant has provided a number of examples of NIMR genes. However, as indicated

above, the Applicant has defined the term "NIMR gene" to include not only the identified NIMR genes, but a genus of molecules including those genes, the genus supposedly defined by a common structure and function.

However, in the present case, the level of structural relatedness required is low. For example, on page 27, the application states that "it will be understood that the level of sequence identity among microbial genes, even though members of the same family, is not necessarily high;" continuing to provide an example demonstrating that such identity may be "less than 20%." In addition, the application also teaches that "structural similarity among NIMR-molecules can also be determined based on "three-dimensional correspondence" of amino acid residues. Id. Such correspondence is found in spatial correspondence, and where residues perform the same function. Thus, while the Applicant has identified a number of examples of NIMR genes and polypeptides, the Applicant has not actually identified any structure that is common to the genus. The Applicant has allowed for a great deal of sequence variation, and for three-dimensional correspondence (of which no exemplary structure has been identified) without sequence identity.

The Applicant has also provided a functional aspect to the definition of NIMR genes. Page 9 of the application states that NIMR polypeptides have an NIMR activity, and page 22 states that NIMR genes encode polypeptide with an NIMR activity. However, while the Applicant has provided examples of such activities (page 9), the specification does not identify any function that is common to all of the NIMR polypeptides, or even a complete list of functions falling with the bounds of an "NIMR activity" Thus, the Applicant has not provided a useful functional definition for a NIMR polypeptide.

Further, as indicated in the MPEP excerpt above, where the Applicant defines a genus by a functional characteristic, that function must be accompanied by a structure to which the function has a known or disclosed correlation. Because the Applicant has provided neither a common structure nor function, the Applicant cannot be said to have provided demonstrated any correlation between NIMR activities and any specific structural characteristic. In view of the above discussion, the Applicant has not provided an adequate written description for any NIMR molecule.

The lack of an adequate description of NIMR modulators is only part of the problem with the rejected claims. The present claims are drawn to modulation of NIMR molecules, and not to the molecules themselves. More specifically, the claims are drawn to methods of using modulators of NIMR molecules. However, the Applicant has provided no examples of such modulators. See e.g., pages 77-89 (describing components of compositions that may be used to deliver such modulators, but providing no examples of the modulators themselves). It is noted that the Applicant has provided assays that would, if one in the art could identify NIMR molecules, be useful in the identification of NIMR polypeptide modulators (pages 59-75). While the Applicant has provided a series of general assays for the identification of potential modulators, the Applicant has not provided any examples of, or guidance to, modulators that may be so identified. No information is provided as to specific compounds or structures that could be used as modulators of NIMR molecules. Thus, the Applicant has not provided adequate written description support for methods of using NIMR modulators because the Applicant has not identified any such compositions.

In addition to the lack of description of specific modulators of NIMR molecules, because the Applicant has not adequately described NIMR molecules, the Applicant has also failed to provide descriptive support for modulators thereof. This is because, if the Applicant has not adequately described the compounds are being modulated such that those in the art would be able to identify the molecules, then those in the art would also be unable to determine what molecules would modulate the activity of the unidentified compounds. There is therefore insufficient written description support in the application to claims on the use of NIMR modulating compounds because there is insufficient written description in the application for the modulators being so used. It is noted that, although the above rejection is discussing the lack of support of modulators of NIMR molecules generally, the same rational also applies as against the elected inventions, comprising the use of modulators of the nfnB NIMR polypeptide.

11. Claims 19, 25, 26, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims have been described above. The claims are rejected on several grounds. First, the application is not enabling for methods of using any modulator of any NIMR polypeptide to decrease the virulence or infectivity of a microbe, or to treat a microbial infection. Second, the Applicant is not enabled for the use of modulators of NIMR polypeptides to reduce the virulence or infectivity of a microbe.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

With respect to the first ground of rejection, that the Applicant is not enabled for the use of any modulator of any NIMR polypeptide, it is noted that, as indicted above, the rejected claims read broadly on the use of any modulator of any NIMR polypeptide to decrease the virulence or infectivity of, or treat infection by, any microbe. However, as indicated above (in the rejection of paragraph 6 of this action), the present application does not provide a complete definition of what comprises a NIMR molecule (i.e. it is not clear that molecules comprise NIMR molecules), or provide any examples or guidance as to what compounds are likely to be effective modulators thereof. While those in the art are likely to be skilled in the art, absent some guidance those skilled in the art would not be able to predict what compounds are likely to be effective NIMR polypeptide modulators. The applicant has not provided any such guidance, or any examples of modulators of NIMR activity.

It is noted that the Applicant has provided general examples of methods to identify such modulators. However, the Applicant has neither identified any particular compounds that can act

as modulators, nor provided any guidance as to what compounds are likely to have the required function. One of ordinary skill in the art attempting to identify such modulators would be faced with a large number of proteins and other compounds that may be potential modulators of one or more of the NNIMR molecules. See e.g., App. page 20, (providing a list of large categories of compounds from which the potential modulators or "test compounds" may be drawn). Because there is no guidance as to what molecules may modulate NIMR functions, the Applicant has left it to those in the art to discover for themselves what compounds would be effective modulators. In view of the limited teachings by the application, and given the large number of potential modulators, and the lack of predictability as to what compounds may have a modulating activity, the Applicant has not provided adequate information such that those in the art may be able to practice the claimed invention without undue experimentation. The identified claims are therefore rejected as lacking enabling support in the specification. Although the above rejection is discussing the lack of enablement of modulators of NIMR molecules generally, the same rational also applies as against the elected inventions, comprising the use of modulators of the nfnB NIMR polypeptide. For the reasons above, the Applicant is not enabled for the use of NIMR polypeptide modulators generally.

The claims are also rejected for lack of enablement because the Applicant has not taught those in the art how to use modulators of NIMR polypeptides to reduce the virulence or infectivity of microbes. In addition to the lack of teachings indicated above with respect to what compounds actually comprise NIMR molecules and modulators thereof, the application also provides little guidance as to which of the NIMR polypeptides are involved in cell virulence or infectivity. While the application provides as generic listing of the functionalities of certain

NIMR molecules (pages 104-107) there is no indication as to which of these molecules, when up or down regulated, would yield a change in the microbe's virulence or infectivity.

As an illustration of the lack of enablement, the following discusses the claimed invention, which involves the modulation of the polypeptide encoded by the nfnB gene. This polypeptide is disclosed on page 105 as an oxygen-insensitive NAD(P)H nitroreductase. It is noted that the art indicates that proteins with this function may be involved with virulence by way of making the cell more or less susceptible to an antibiotic. See e.g., Kwon et al., Antimicrob Agents Chemother 44(8): 2133-42 (teaching that modulation of polypeptides with this function can make a bacterium more or less susceptible to the antibiotic metronidazole). However, there does not appear to be any evidence that the functionality of this polypeptide affects the ability of the microbe to infect a host. Thus, the Applicant has not demonstrated that modulators to this polypeptide would be capable of reducing the infectivity of the microbe.

Furthermore, the application indicates that the nfnB gene is upregulated by the mar gene. However, the application does not indicate what the result of this upregulation is. For example, from the application, it would appear that, because the mar regulon upregulates the nfnB gene, the upregulation of this gene would increase the virulence of the cell. However, the Kwon reference (supra, page 2134) teaches that the upregulation of the rdxA gene (a homologue with the same general function as the nfnB gene, Goodwin et al., Molec Microbiol 28(2): 383-93, at 384) would actually increase the cell's susceptibility to antibiotics, thereby demonstrating that the upregulation of this gene actually reduces the cell's virulence. Thus, assuming those in the art were in possession of a compounds capable of modulating the function of this polypeptide, they would not know when it would be appropriate to either increase or decrease the function of the

target gene/polypeptide to achieve the desired result. Because the Applicant has not indicated or provided any guidance as to which NIMR polypeptides would have what, if any, effect on microbial virulence or infectivity, the Applicant has not enabled those in the art to practice the claimed methods.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 19, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Goodwin et al. (Molec Microbiol 28(2): 383-93). These claims read on methods of reducing the virulence of a microbe by administering to the microbe an agent that modulates the activity of a NIMR polypeptide, and exposing the microbe to an environmental challenge. The application indicates that the NIMR polypeptides include polypeptides that are structurally related to the polypeptides encoded by the genes identified on pages 7-8. See, App., page 9 first and second paragraphs. The application also identifies as an environmental challenge the contacting of the microbe with an antibiotic. Pages 9-10, esp., page 10 second paragraph. Thus, the claim reads on methods of reducing the virulence of a microbe comprising administering to the microbe a NIMR modulator and an antibiotic.

Goodwin teaches the transformation of E coli cells with vectors for the expression of the H. pylori rdxA gene. Page 384, right column. This gene is described in the reference as a homologue of the E coli nfnB gene. Id. The reference also teaches the transformed E coli were cultured in media containing the antibiotic metronidazole (Mtz) to determine the effect of the transformation. Pages 385-86, and 391. Thus, the reference teaches the use of modulator of the rdxA activity (the vector encoding the polypeptide for expression- thereby increasing expression and activity of the polypeptide in the transformed cell) and the exposure of the cell to an environmental challenge (Mtz), thereby resulting in cells with increased susceptibility to Mtz, and with decreased virulence (the cells are killed).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 19, 25, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Goodwin in view of Drabek et al. (Gene Ther 4(2): 93-100). The rejected claims read on methods of reducing the virulence of a microbe by administering to the microbe an agent that modulates the activity of a NIMR polypeptide, including where the NIMR polypeptide is that of nfnB, and exposing the microbe to an environmental challenge (e.g., an antibiotic). For

the purposes of this action, the claim is being read such that the polypeptide is that encoded by the nfnB gene of E. coli K-12.

The teachings of Goodwin have been described above. The reference teaches that the administration of a plasmid encoding the NADPH nitroreductase had the effect of rendering the cell more susceptible to the antibiotic. Thus, when the cells were exposed to the antibiotic, they were killed, rendering them less virulent. The reference also teaches that the rdxA gene is a homologue of the nfnB gene. Page 384, right column. The reference therefore teaches the inventions of claims 19 and 25, but does not teach the use claimed method wherein the NIMR polypeptide being modulated is that encoded by the nfnB gene, although Goodwin does indicate that the teachings of the rdxA gene are relevant to the nfnB gene.

Drabek teaches the transformation of and expression in a eukaryotic cell of the nfnB gene (referred to as NTR in the reference) in a eukaryotic cell. Page 93. The reference teaches that the transformation with and expression of this gene caused the transformed cell to become susceptible to the prodrug CB1954. This is because the encoded enzyme, when expressed in the cell and when cultured in the presence of the prodrug, resulted in the processing of the prodrug by the encoded enzyme, making it toxic to the cell. Thus, the teachings of the Drabek reference indicate that the nfnB gene may be used in a similar manner to that of the rdxA gene as described in Goodwin. It would therefore have been obvious to those in the art to render a bacterial cell susceptible to the prodrug CB1954 by transforming it with a vector comprising the nfnB gene. Those in the art would have had a reasonable expectation of success in such a transformation given the teachings of both Drabek and Goodwin indicating that rdxA is a homologue of nfnB, thus indicating that the two genes may be used in a similar manner.

Conclusion

16. No claims are allowed.

17. The following prior art reference is made of record and is considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Whiteway et al., J Bacteriol 180(21): 5529-39. This reference is considered relevant to the claims for the same reasons as is Goodwin. The reference is considered redundant thereto. See, e.g., Goodwin, page 384, indicating that the rdxA, nfnB, and nfsB genes are all homologues.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 1/12/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600